Food Safety and Nutrition

- Development of SRMs for Dietary Supplements
- Development of Ephedrine Alkaloid-Based Dietary Supplement Standard Reference Materials

Program: Food Safety and Nutrition

Title: Development of Standard Reference Materials (SRMs) for Dietary Supplements

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Abstract: The Analytical Chemistry Division is collaborating with the Food and Drug Administration (FDA), and the National Institutes of Health's Office of Dietary Supplements (NIH-ODS) in a multi-year program to develop Standard Reference Materials (SRMs) and analytical methods for a number of dietary supplement materials, including botanical and botanical-containing matrices as well as a multivitamin/multielement material. The first botanical dietary supplement SRMs, consisting of a suite of five ephedra-containing materials (ground dried plant, two extracts, diet pills, and protein drink powder), were completed in 2004. Measurements are currently in progress for the *Ginkgo biloba* SRM suite (plant, extract, and tablet). Acquisition of additional materials, including saw palmetto, bitter orange, carrot oil, and St. John's wort, was initiated in 2004. SRM 3280, Multivitamin/Multielement Tablets was prepared, and measurements were initiated for value assignment of 18 elements, 15 vitamins, and a carotenoid.

Purpose: The enactment of the Dietary Supplement Health and Education Act (DSHEA) in 1994 by the U.S. Congress has promoted growth in the nutritional supplement industry, due in part to the way in which dietary supplements are regulated. DSHEA provides a legal definition of dietary supplements that classifies these materials separately from food additives and pharmaceutical drugs. Requirements for product labeling are less stringent than for drugs, and the burden of proof for the safety of dietary supplements is placed on the Food and Drug Administration (FDA). More than 50% of the U.S. population uses dietary supplements, accounting for roughly $10 billion in sales every year. A variety of botanical-containing products are marketed as dietary supplements, e.g., St. John's wort, ginkgo, saw palmetto, and green tea. Botanical reference materials with assigned values for active and/or marker compounds are needed to address two primary concerns in the botanical dietary supplements community: safety and efficacy. Potential health risks may result from contamination (e.g., pesticides, toxic elements), adulteration (presence of unlabeled foreign materials including pharmaceuticals), or variability in product composition (e.g., changes in levels of active constituents). Secondly, product quality and consistency must be maintained through verification of dietary supplement label claims. These needs can be addressed by the development of analytical methods and reference materials to support chemical composition measurements for dietary supplements.

In 2001 the Analytical Chemistry Division (ACD) of NIST, FDA, and NIH-ODS initiated a multi-year program to develop Standard Reference Materials (SRMs) and analytical methods for a number of botanical and botanical-containing dietary supplements. The goal of this collaborative program is to provide SRMs for eight to ten different botanical dietary supplements over a six-year period. NIH-ODS is also collaborating with the U.S. Department of Agriculture (USDA) to establish the Dietary Supplement Ingredient Database (DSID). The DSID project will report the results of a systematic survey of supplement composition, including chemical composition of ingredients with the primary focus on vitamin and mineral supplements. To

support the DSID project, ACD and NIH-ODS have expanded their collaboration to develop dietary supplement matrix SRMs to include a multivitamin/multielement supplement. SRM 3280 Multivitamin/Multielement Tablets is a commercial multivitamin/multielement tablet which will be value assigned for concentrations of 18 elements and 15 vitamins and carotenoids for which label claims are made.

Major Accomplishments: Based on NIH-ODS priorities and needs, ACD is developing SRMs for the following botanical dietary supplement materials: ephedra, G*inkgo biloba*, saw palmetto, bitter orange, green tea, St. John's wort, ∃-carotene and tocopherol mixtures, and multivitamin/multielement tablets. Each botanical material SRM will consist of a suite of matrices including plant, extract, and finished product. The first SRM suite for ephedra-containing dietary supplements (SRMs 3240-3244) has been completed (see Technical Report xxxx). The second SRM suite for *Ginkgo biloba* has been prepared and measurements of ginkgolides and flavonoids are nearing completion. Plant and extract materials for the next suites, saw palmetto and bitter orange, were obtained in 2004; a carrot oil, representing a natural carotene mixture, was also obtained. The candidate material for the multivitamin/multielement tablet SRM was received in mid-2004, and methods development and measurements are currently underway.

Impact: The availability of botanical dietary supplement matrix SRMs with certified concentrations of active/marker constituents and contaminants and a multivitamin/multielement tablet SRM will provide the measurement tools necessary to assess the quality of dietary supplements.

Future Plans: This program is a six-year effort to develop SRMs for eight to ten different botanical dietary supplements. After completion of the ephedra and ginkgo SRM suites, the next materials targeted for development of SRMs are: saw palmetto, bitter orange, ∃-carotene in carrot oil, St. John's wort, green tea, and tocopherol mixtures. Acquisition of the St. John's wort and green tea are in progress and will be completed in early 2005. The next priorities for SRM development include: β-carotene (e.g., a mixture of β-carotene isomers), vitamin E (e.g., d-α-tocopheryl acetate/d,l-α-tocopheryl acetate and a mixture of the tocopherol and tocotrienol isomers), black cohosh, and a number of berry materials (e.g., cranberries and blueberries). Completion of the multivitamin and multielement SRM is scheduled for early 2006.

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Title: Development of Ephedrine Alkaloid-Based Dietary Supplement Standard Reference Materials (SRMs)

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Abstract: A suite of five ephedra-containing dietary supplement Standard Reference Materials has been issued with certified values for ephedrine alkaloids, synephrine, caffeine, and selected toxic trace elements. The materials represent a variety of natural, extracted, and processed sample matrices, which provide different analytical challenges. The constituents have been determined by multiple independent methods with measurements performed by NIST and by three collaborating laboratories. The methods utilized different sample extraction and cleanup steps in addition to different instrumental analytical techniques and approaches to quantification. In addition, food-matrix proximates were determined by National Food Processor Association (NFPA) laboratories, for one of the ephedra-containing SRMs. The SRMs are primarily intended for method validation and for use as control materials to support the analysis of dietary supplements and related botanical materials.

Purpose: The enactment of the Dietary Supplement Health and Education Act (DSHEA) in 1994 by the U. S. Congress has promoted growth in the nutritional supplement industry, due in part to the way in which dietary supplements are regulated. DSHEA provides a legal definition of dietary supplements, which classifies these materials separately from food additives and pharmaceutical drugs. Requirements for product labeling are less stringent than for drug substances, and the burden of proof for the safety of dietary supplements is placed on the Food and Drug Administration (FDA). In December 2003, the FDA issued a ruling that declared dietary supplements that contain ephedrine alkaloids to be adulterated. This ruling was based on mounting evidence of health risks associated with the use of ephedra, and in effect bans the use of ephedrine alkaloids (regardless of their botanical origin) in dietary supplements. Ephedra-containing dietary supplement SRMs are intended for use in method validation and as control materials for analytical methods used in the determination of ephedrine alkaloids, and should prove to be useful to support such methods and to demonstrate the absence of ephedrine alkaloids in ephedra-free products.

Major Accomplishments: NIST, working in collaboration with the National Institutes of Health Office of Dietary Supplements (NIH-ODS) and FDA, Center for Drug Evaluation and Research (CDER) and Center for Food Safety and Applied Nutrition (CFSAN), has recently issued a suite of Standard Reference Materials® (SRMs) that contain ephedra. Five SRMs are available: SRM 3240 *Ephedra sinica* Stapf Aerial Parts, SRM 3241 *Ephedra sinica* Stapf Native Extract, SRM 3242 *Ephedra sinica* Stapf Commercial Extract, SRM 3243 Ephedra-Containing Solid Oral Dosage Form, and SRM 3244 Ephedra-Containing Protein Powder. In addition, SRM 3245 Ephedra Suite is available and contains two bottles each of the five ephedra-containing materials. The SRMs are certified for levels of ephedrine alkaloids and selected toxic trace elements (As, Cd, Hg, and Pb). In addition, the level of synephrine (an ephedrine-like alkaloid present in many ephedra-free dietary supplements) is certified in SRM 3243, and levels of

caffeine are certified in SRM 3243 and SRM 3244. Information on proximates (i.e., moisture, solids, ash, protein, carbohydrates, fat) and nutrient elements is also included with SRM 3244.

Impact: SRMs 3240 through 3244 represent the first in a series of dietary supplement SRMs to be offered by NIST with certified values for organic constituents and selected trace elements. These materials are provided primarily for use in method development and as control materials to support analytical methods for the determination of these constituents. In the absence of a formal regulatory environment, the SRM suites will assist manufacturers of dietary supplements to characterize raw materials voluntarily and to prevent the use of materials that are contaminated or adulterated. In addition, the SRMs will assist self-assessment of consistency and quality in finished products. The goal of this ongoing effort is to provide tools to the dietary supplement industry and measurement communities that will lead to improved quality of dietary supplements, and ultimately reduce public health risks that could potentially be associated with these products.

Future Plans: The development of dietary supplement SRMs is an ongoing effort. SRMs based on multivitamin/mineral tablets, *ginkgo biloba*, saw palmetto, bitter orange, green tea, St. John's wort, and carrots (carotenes) are in progress.

Figure 1. Photograph of voucher specimen representative of plants used in the preparation of SRM 3240 *Ephedra sinica* Stapf Aerial Parts